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Director of RWS Group plc, of Europa House, Marsham Way, Gerrards Cross,  
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2. That the translator responsible for the attached translation is well acquainted with the German and English languages.
3. That the attached is, to the best of RWS Group plc knowledge and belief, a true translation into the English language of the accompanying copy of the specification filed with the application for a patent in Germany on 28 December 1998 under the number 198 60 373.8 and the official certificate attached hereto.
4. That I believe that all statements made herein of my own knowledge are true and that all statements made on information and belief are true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the patent application in the United States of America or any patent issuing thereon.

For and on behalf of RWS Group plc

The 2nd day of April 2003

**FEDERAL REPUBLIC OF GERMANY**

**Certificate**

Aventis Research & Technologies GmbH & Co KG

of

Frankfurt am Main/Germany

have filed a Patent Application under the title:

“Oral hygiene product comprising spherical microparticles based on unbranched water-insoluble polyglucans”

on 28 December 1998 at the German Patent and Trademark Office.

The attached document is a correct and accurate reproduction of the original submission for this Patent Application.

The German Patent and Trademark Office has for the time being given the Application the symbol A 61 K 7/16 of the International Patent Classification.

Munich, 17 September 1999

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The President

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File No: 198 60 373.8

## Description

Oral hygiene product comprising spherical microparticles based on unbranched water-insoluble polyglucans

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The present invention relates to an oral hygiene product which comprises, as essential constituent, spherical microparticles based on unbranched water-insoluble polyglucans.

10 The use of polyglucans in an oral hygiene product, in particular toothpaste and chewing gums for dental hygiene, has long been known.

However, polyglucans are a very heterogeneous class of compounds whose individual representatives have the most varied properties. A known  
15 example of the polyglucan which is widely distributed in nature is starch. Starch consists of two different polyglucans, amylose and amylopectin, whose proportion varies considerably depending on the origin of the starch. Amylose is a water-soluble unbranched 1,4-linked poly- $\alpha$ -glucan having a molecular weight of from about 50,000 to 150,000. Amylopectin, in  
20 contrast, is water-insoluble and has a highly branched structure having 1,4 and 1,6 links and a molecular weight of from 300,000 to 2,000,000. A further frequently accounted polyglucan is cellulose, which is water-insoluble and, in contrast to starch, is  $\beta$ -1,4 linked.

25 Starch or its constituents are used in oral hygiene products, inter alia, as gelling agent, filler, thickener or binder. For example, EP-B-0 502 895 describes a thickener for toothpastes which, in addition to an unbranched polymer nonstarch compound such as cellulose and its derivatives, for example carboxymethyl cellulose or hydroxyethyl cellulose, comprises a  
30 branched starch. Branched starch denotes here a starch which consists of at least 70% branched polyglucans and preferably has a molecular weight of from 1,000,000 to 2,000,000.

It is known to derivatize starch or its polyglucan constituents to achieve  
35 certain properties.

Thus US patent 5,009,882 relates to the use of a carboxylated starch in oral hygiene products such as toothpastes or mouthwashes to prevent plaque formation. The starch molecule described here is composed of non-carboxylated glucan blocks and carboxylated glucan blocks having a degree of carboxylation of from 1 to 3, the carboxylation taking place with ring opening of the glucan unit.

EP-A-0 673 605 proposes a particulate matrix as support for a flavoring such as lemon oil, which is intended to improve the storage stability of the flavoring, for example in toothpastes and chewing gums for oral hygiene. The matrix consists of a mixture of a hydrogenated starch hydrolysate and maltodextrose, the hydrogenated starch hydrolysate being a polyol having a degree of polymerization of a maximum of 4, one terminal glucan unit of which being hydrolytically opened.

Although a multiplicity of varying oral hygiene products are already available, the development of new improved products is of great importance, since the most effective protection against caries and periodontosis is still careful cleaning of the teeth with suitable products.

Thus tooth cleaning products such as toothpastes, tooth powders and chewing gums should clean gently without abrasive action in order to protect the enamel. A prerequisite is that no components which can act abrasively are present in these products.

To improve the hygiene properties, frequently the most varied active compounds are added to oral hygiene products. In order for these active compounds to be fully effective, it is advantageous to incorporate these into a suitable matrix which ensures optimal release at the target location. Quite generally, such products should retain their consistency and effectiveness even over a relatively long storage period.

For the inventive oral hygiene products, the use of spherical microparticles which consists in whole or in part of at least one water-insoluble unbranched polyglucan is essential.

For the present invention, oral hygiene products denote both products which either serve solely for cleaning the oral cavity and thus are to be included with cosmetics, and products which on account of additional active compounds having specific preventative and curative properties at

the same time also have therapeutic purposes and may therefore be considered as medicaments.

5 Examples of oral hygiene products are mouthwashes, mouth powders, mouth pills, mouth sprays, denture hygiene products, prosthesis hygiene products and dental hygiene products, such as toothpastes, tooth gels, tooth cleaning powders and chewing gums for improving oral hygiene, but also plaque disclosure tablets for visualizing dental plaque, for example as a check.

10

The microparticles inventively used in oral hygiene products are distinguished in particular by their multifunctionality and can be used and adapted for the most varied uses, so that using them oral hygiene products for the most varied applications can be obtained specifically.

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Thus the microparticles can replace quite generally the conventional polyglucans previously used in oral hygiene products and take over their function as thickener, binder, filler or gelling agent.

20

Further, they have an outstanding cleaning and polishing action and are therefore particularly suitable as cleaning and polishing agents, for example for mechanical tooth, denture and prosthesis cleaning.

25 The inventively used microparticles have, in addition to their regular spherical shape, a very high dispersability.

It has been found that even without adding further aids, such as dispersants, a stable dispersion can form which remains stable even over a relatively long period.

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Thus they can form, for example, stable emulsions, aerosols or suspensions. This property is of particular importance for the production of suitable formulations for oral hygiene products, since the use of dispersants can frequently be avoided, or the amount of dispersants can be decreased, as a result of which the production can be simplified and made cheaper.

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Of particular importance for dental hygiene are toothpastes, termed gel in transparent form, which, owing to their content of cleaning and polishing elements and surface-active substances, optimize the plaque-removing action of toothbrushes and, if appropriate, apply active compounds such as fluoride which act to protect tooth and periodontum.

Owing to their uniform spherical shape having no, or only a few, surface roughnesses without great irregularities such as projections, corners or edges, the inventively used microparticles do not have an abrasive action and can therefore be used advantageously in dental hygiene products.

In addition, the microparticles are an excellent carrier material for active compounds, such as healing or hygiene substances, flavorings etc.

The active compound can be added to the starting compounds used for producing the microparticles so that that microparticles are a mixture of starting compound and active compound.

The active compound can be encapsulated to the microparticles, in which case customary encapsulation techniques can be used. Suitable examples are emulsion processes or spray-drying processes. The latter term also includes spraying processes in which the particles are sprayed with a solution of active compound in a fluidized bed or similar processes.

In addition, the active compound can be absorbed and/or adsorbed to the microparticle surface by suspending, for example the active compound and the microparticles, in a suitable medium, allowing it to stand to establish equilibrium and then separating off the particles loaded with active compound.

If required, the inventively used microparticles can be configured for controlled release of active compound.

Controlled release of active compound is taken to mean the active compound is not released immediately all at once, but that the release takes place over a defined time and/or after expiry of a defined time period. The release rate can be chosen as desired as a function of the desired application. It can be constant over the period, or it can be high at the start,

followed by a slow release. Controlled release of active compound can be advantageous, for example, for cleaning products for dentures and prostheses which act on the dentures or prostheses over a relative long period of time, for chewing gums, in order to achieve uniform action and persistent taste, or for targeted local administration in the oral cavity, in the throat, to the teeth, etc., which can also be summarized under the terms "mucosal" or "buccal" uses, for example also in the form of what are termed drug delivery systems.

Clearly, the release rate and the rate of degradation of the microparticles are highly dependent on the type of starting materials of the active compound used, on the particle size and the production process. According to requirements, those skilled in the art can produce a system tailored made for its specific application by simple routine variations of these parameters.

The use of the inventively used microparticles as products for the controlled release of active compounds is described extensively by the applicant's German application which was not published prior to the present application and has the official file number 198 16 070.4 "Retard tablet produced from unbranched water-insoluble polysaccharides", which is expressly incorporated here by reference.

Because of its good dispersability and suitability as carrier material, aerosol-based mouth sprays can advantageously be obtained by means of the inventively used microparticles.

Spherical microparticles are taken to mean microparticles which have an approximately spherical shape. When a sphere is described by spatially orientated axes of the same length which depart from a common origin and define the radius of the sphere in all spatial directions, for the spherical particles a deviation of the lengths of the axes from the ideal state of the sphere of from 1% to 40% is possible. Preferably, the deviation is 25% or less, particularly preferably 15% or less.

The microparticles can have a mean diameter  $D_n$  (number average) of from 1 nm to 100  $\mu\text{m}$ , preferably from 100 nm to 15  $\mu\text{m}$ , and particular preferably from 300 nm to 3  $\mu\text{m}$ .

It is clear that depending on the type of the oral hygiene product, the mean diameter can vary.

- 5 For the use in oral hygiene products, small microparticles are particularly suitable which have a mean diameter of 15  $\mu\text{m}$  or less.

The surface of the spherical particles can be compared macroscopically with a raspberry, the depth of irregularities on the particle surface, such as  
10 dents or cuts, is a maximum of 20%, preferably 10%, of the mean diameter of the spherical microparticles.

The specific surface area of the microparticles is generally from 1  $\text{m}^2/\text{g}$  to 100  $\text{m}^2/\text{g}$ , preferably from 1.5  $\text{m}^2/\text{g}$  to 20  $\text{m}^2/\text{g}$ , and particularly preferably  
15 3  $\text{m}^2/\text{g}$  to 10  $\text{m}^2/\text{g}$ .

In addition, the inventively used particles preferably have a dispersity  $D =$  weight average mean of the diameter ( $d_w$ )/number average mean of the diameter ( $d_n$ ) from 1.0 to 10.0, in particular from 1.5 to 5.0, and particularly  
20 preferably from 2.0 to 3.0.

The means used here are defined as follows:

$d_n = \sum n_i \times d_i / \sum n_i = \text{number average}$   
25

$d_w = \sum n_i \times d_i^2 / \sum n_i \times d_i = \text{weight average}$

$n_i = \text{number of particles of diameter } d_i,$

30  $d_i = \text{a defined diameter,}$

$i = \text{serial parameter.}$

In this context, the term weight denotes a weighted mean, as a result of  
35 which the larger diameters have a higher importance.



For the present invention, microparticles can also be used whose surface has been modified, for example by derivatizing functional groups such as the hydroxyl groups of the polyglucan starting compound.

- 5 Unbranched water-insoluble polyglucans in the context of the present invention are polysaccharides which are made up from glucans as monomeric building blocks in such a manner that the individual building blocks are always linked to one another in the same manner. Each basic unit or building block thus defined has exactly two links, each one to
- 10 another monomer. Exceptions from these are only the two basic units which form the start and end of the polysaccharide. These have only one link to a further monomer and form the end groups of the unbranched polyglucan.
- 15 If the basic unit has three or more links, this is described as branching. The degree of branching is given by the number of hydroxyl groups per 100 basic units which do not participate in the structure of the unbranched polymer backbone and which form the branches.
- 20 According to the invention the unbranched water-insoluble polyglucans have a degree of branching of the maximum of 8%, that is to say they have a maximum of 8 branches per 100 basic units. Preferably, the degree of branching is less than 4%, and in particular a maximum of 2.5%.
- 25 Particular preference is given to polyglucans whose degree of branching in the 6 position is less than 4%, preferably a maximum of 2%, and in particular a maximum of 0.5%, and in the other positions, for example in the 2 or 3 position, is preferably in each case a maximum of 2%, and in particular 1%.
- 30 Particular preference is also given to polyglucans having a branching in the 6 position of less than 0.5%.  
Suitable polyglucans for the invention are in particular those which do not have branches or their degree of branching is so minimal that it is no longer detectable by conventional methods.
- 35 Examples of preferred water-insoluble unbranched polyglucans are unbranched poly-D-glucans, the type of linkage being unimportant, provided that unbranching within the meaning of the invention is present.

Examples are poly-alpha-D-glucans, in particular poly(1,4-alpha-D-glucan), and poly(1,3-beta-D-glucans).

5 For the present invention, the prefixes "alpha", "beta" or "D" relate solely to the links which form the polymer backbone and not to the branches.

10 The term "water-insoluble polyglucan", for the purposes of the present invention, is taken to mean compounds which, according to the definition of the German Pharmacopoeia (DAB = Deutsches Arzneimittelbuch, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, Govi-Verlag, Frankfurt, [lacuna] Edition, 1987), in accordance with classes 4 to 7, come under the categories of "poorly soluble", "sparingly soluble", "very sparingly soluble" or "virtually insoluble" compounds.

15 In the case of the inventively used polyglucans, this means that at least 98% of the amount used, in particular at least 99.5%, is insoluble in water under standard conditions ( $T = 25^{\circ}\text{C} \pm 20\%$ ,  $p = 101325 \text{ Pascals} \pm 20\%$ ) (in accordance with classes 4 and 5).

20 For the present invention, sparingly soluble to virtually insoluble compounds, in particular very sparingly soluble to virtually insoluble compounds, are preferred.

25 "Very sparingly soluble" in accordance with class 6 can be illustrated by the following experimental description:

30 One gram of the polyglucan under test is heated in 1 l of deionized water to  $130^{\circ}\text{C}$  under a pressure of 1 bar. The resultant solution remains stable for only a short time over the course of a few minutes. During cooling under standard conditions, the substance precipitates out again. After cooling to room temperature and separating off by centrifugation, taking into account the experimental losses, at least 66% of the amount used can be recovered.

35 The inventively used polyglucans can be of any origin, provided that the above specified conditions with respect to the terms "unbranched" and "water-insoluble" are complied with.

They can be obtained naturally or by bioengineering routes.

For example, they can be obtained from natural vegetable or animal sources by isolation and/or purification.

5 Sources can also be used which have been genetically modified in such a manner that, compared with the unmodified source, they have a high content of unbranched or relatively slightly branched polyglucans.

They can also have been prepared from branched polyglucans by enzymatic or chemical debranching.

10 In this case, branched polyglucans which contain the branches are treated with an enzyme in such a manner that the branches are cleaved, so that after their removal unbranched polyglucans are present. These enzymes can be, for example, amylases, isoamylases, gluconohydrolases [sic], cyclomaltodextrin-glucanotransferases or pullulanases.

15 Bioengineering methods comprise biocatalytic and biotransformatory processes, or fermentative processes.

20 Unbranched polyglucans prepared by biocatalysis (also: biotransformation) in the context of this invention means that the unbranched polyglucan is prepared by catalytic reaction of monomeric basic building blocks such as oligomeric saccharides, for example of monosaccharides and/or disaccharides, by using what is termed a biocatalyst, customarily an enzyme, under suitable conditions. In this context, "in vitro biocatalysis" is  
25 also mentioned.

Unbranched polyglucans from fermentations are, within the linguistic usage of the invention, unbranched polyglucans which are obtained, or can be obtained with the inclusion and conjoint use of fermentative processes, by  
30 fermentative processes with the use of naturally occurring organisms, such as fungi, algae, bacilli, bacteria or protists, or using organisms which do not naturally occur, but natural organisms modified with the use of generally defined genetic engineering methods, such as fungi, algae, bacilli, bacteria or protists. In this context, "in vivo biocatalysis" is also mentioned.

35 Examples of such microorganisms are *Piichia pastoris*, *Trichoderma reseii*, *Staphylococcus carnosus*, *Escherichia coli* or *Aspergillus niger*.

Advantageous processes for bioengineering production are described, for example, in WO 95/31553 or the applicant's German patent application having the official file number 198 27 978.5, which was not published prior to the present application.

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According to WO 95/31553, amylsucrases are used for preparing unbranched water-insoluble polyglucans, such as poly-1,4- $\alpha$ -D-glucan, using a biocatalytic process.

Further suitable enzymes are polysaccharide synthases, starch synthases, glycol transferases, 1,4- $\alpha$ -D-glucan transferases, glycogen synthases and phosphorylases.

Modified water-insoluble unbranched polyglucans can also be used, in which case the polyglucans can have been chemically modified, for example, by esterification and/or etherification in one or more positions which do not participate in the unbranched linkage. In the case of the preferred 1,4-linked polyglucans, the modification can take place in the 2, 3 and/or 6 position.

Modification within the meaning of the invention means that the hydroxyl groups present that do not take part in the linkage are chemically modified. This excludes ring opening of the glucan units, as takes place, for example, in oxidative carboxylation or hydrolysis. Measures for such modifications are long known to those skilled in the art.

25

Thus, unbranched polyglucans such as pullulans, which are themselves water-soluble, can be made water-insoluble by modification.

For the present invention, preferably, water-insoluble unbranched polyglucans are used which have been prepared in a bioengineering process, in particular in a biocatalytic or a fermentative process, biocatalytically prepared polyglucan being particularly preferred.

In contrast to polyglucans which are isolated from natural sources, such as plants, the unbranched water-insoluble polyglucans obtained in this case have a particularly homogeneous property profile, for example with respect to the molecular weight distribution, they contain no unwanted byproducts which have to be removed in a complex manner or could trigger allergic

reactions, or at any rate only contain them in very small amounts, and can be reproduced in a simple manner to exact specifications.

5 Although comparatively homogeneous products can also be obtained by chemical or enzymatic debranching, in many cases a residue of undebranched or only inadequately debranched starting material remains which can only be removed with difficulty.

10 Bioengineering methods, and in particular biocatalytic methods, have the advantage that water-insoluble unbranched polyglucans can be obtained directly, such as, for example, the preferred poly-1,4- $\alpha$ -D-glucans, which contain no branches, or their degree of branching is below the limit of detection with customary analytical methods.

15 In addition, the polyglucans can be used in the form of what are determined alpha-amylase-resistant polyglucans, as described, by the example of poly-1,4- $\alpha$ -D-glucan in the applicant's German patent application having the official file number 198 30 618.0, which was not published prior to the present application.

20

Alpha-amylase-resistant polyglucans can be obtained by preparing a suspension or dispersion of water-insoluble polyglucans and water, heating the suspension or dispersion to a temperature in the range from 50 to 100°C, allowing the resultant gel-like mixture to cool to a temperature in the  
25 range from 50°C to freezing point, preferably 35 to 15°C, 27 to 22°C, 16 to 0°C or 6 to 2°C, over a period of from 1 to 72 h, preferably from 1 to 36 h, and in particular 15 to 30 h, and retrograding the gel-like mixture at a temperature which is lower than the temperature of the heated gel-like mixture in a temperature range of 90 to 4°C, and if appropriate drying or  
30 dewatering the resultant product.

The polyglucan can also be used as thermoplastic polyglucan, which is obtainable by melting unbranched water-insoluble polyglucan and adding at least 20% by weight, preferably at least 30% by weight, of a plasticizer  
35 such as sorbitol, glycerol, its condensation products and oligomers, DMSO, succinic acid, citric acid monohydrate, maleic acid, tartaric acid etc., at approximately 170°C.

The applicant's German patent application having the official file number 198 30 618.0 which was not published prior to the present application and is expressly incorporated herein by reference describes suitable measures and properties of thermoplastic polyglucans as exemplified by the preferred unbranched water-insoluble poly(1,4- $\alpha$ -D-glucan)s.

5 The molecular weights  $M_w$  (weight average, determined by gel permeation chromatography in comparison with a calibration by pullulan standard) of the inventively used unbranched polyglucans can vary in a wide range from  $0.75 \times 10^2$  g/mol to  $10^7$  g/mol. Preferably, the molecular weight  $M_w$  is in a  
10 range from  $10^3$  g/mol to  $10^6$  g/mol and particularly preferably from  $10^3$  g/mol to  $10^5$  g/mol. A further advantageous range is from  $2 \times 10^3$  to  $8 \times 10^3$ . Corresponding ranges apply for the preferably used poly-1,4-D-glucan.

The molecular weight distribution or polydispersity  $M_w/M_n$  can also vary in  
15 wide ranges, depending on the polyglucan preparation process. Preferred values are from 1.01 to 50, in particular from 1.01 to 15, with small polydispersity values being particularly preferred, for example from 1.01 to 2.5. In this case the polydispersity increases with a bimodal distribution of the molecular weights.

20

For preparing the microparticles, a single polyglucan, in particular poly-1,4-D-glucan, and very particularly poly-1,4- $\alpha$ -D-glucan or mixtures of two or more representatives, can be used.

25 In a further embodiment, a water-insoluble branched polysaccharide, preferably a polyglucan, in particular a poly-1,4- $\alpha$ -D-glucan, or a poly-1,3- $\beta$ -D-glucan, can be added.

Mixtures of two or more branched polysaccharides can also be added.

30 The branched polysaccharides can be of any origin. In this context, reference is made to the descriptions in this respect for the unbranched water-insoluble polyglucans. Preferred sources are starch and starch analogs such as glycogen. If necessary, the content of unbranched structures in the branched polysaccharides can be increased by suitable  
35 enrichment processes.

The same specifications apply for the water insolubility as for the unbranched water-insoluble polyglucan. The molecular weight for the

branched polysaccharides can also be higher, for example can have values up to preferably  $10^9$  g/mol or more.

5 Other polymers, in particular biocompatible or biodegradable polymers can also be admixed. In this case the amount of the polymer or of the other polymers which are admixed without the spherical shape and/or other properties of the microparticles to be prepared being changed always depends on the added polymer.

10 To ensure the desired properties of the microparticles, the proportion of unbranched water-insoluble polyglucan should be at least 70% by weight, in particular 80% by weight, and preferably 90% by weight, based on the total content of unbranched water-insoluble polyglucan, including, if appropriate, branched polysaccharide and, if appropriate, other polymers.

15 According to a particularly preferred embodiment, 100% by weight of the microparticles consist of unbranched water-insoluble polyglucan, in particular unbranched water-insoluble poly-1,4- $\alpha$ -D-glucan, which is preferably being obtained biocatalytically.

20 Examples of processes for preparing the microparticles are the precipitation process or spray-drying processes.

25 The spherical microparticles can be prepared by dissolving the water-insoluble unbranched polyglucan or a mixture of a plurality thereof and, if appropriate, other polymers, in a solvent, for example DMSO, introducing the solution into a precipitant, for example water, preferably at a temperature of 20°C to 60°C, if necessary cooling the solution to a temperature of -10°C to +10°C and separating off the particles thus  
30 formed.

In this case the polyglucan used as starting material can be dissolved at room temperature or higher temperatures.

35 The concentration of unbranched water-insoluble polyglucan including, if appropriate, a branched polysaccharide and other polymers, in the solvent can be varied according to requirements within broad limits. Preferably, it is in a range from 0.02 g/ml to 1.0 g/ml, in particular from 0.05 g/ml to 0.8 g/ml, and particularly preferably from 0.3 g/l [sic] to 0.6 g/l [sic].

Examples of precipitants are water, dichloromethane, a mixture of water and dichloromethane, mixtures of waters and alcohols, such as methanol, ethanol, isopropanol, in which case water and a mixture of water and dichloromethane [sic] are particularly preferred.

Preferably, the ratio of solvent to precipitant is selected in a range from 1:1000 to 1:4 (part of solvent/parts of precipitant), preferably 1:100 to 1:10, and in particular 1:70 to 1:30.

Generally, it is immaterial in which sequence the solvent and the precipitant are combined, that is to say whether the precipitant is added to the solvent or vice versa. However, it is of importance that rapid mixing is ensured.

The precipitation process can be carried out relatively slowly at low temperature overnight.

It can be influenced and controlled by varying the temperature and the precipitant.

If cooling is carried out, it should be ensured that the mixture of solvent and precipitant remains liquid and does not freeze.

By the conjointure of suitable additives, the properties of the microparticles such as size, surface structure, porosity etc., and the process procedure, can be affected.

Suitable additives are, for example, surfactants such as sodium dodecylsulfate, N-methylgluconamide, polysorbates (for example Tween (registered trademark)), alkylpolyglycol ether, ethyleneoxide-propyleneoxide block polymers (for example Pluronic (registered trademark)), alkyl polyglycol ether sulfates, in general alkylsulfates and fatty acid glycol esters, and sugars, for example fructose, sucrose, glucose, water-soluble cellulose or hot-water-soluble poly-alpha-D-glucan, for example native or chemically modified starches, poly-alpha-D-glucans produced from these starches, and starch-analog compounds.

Customarily, these additives are added to the precipitant. The amount used depends on the respective individual case and the desired particle properties, determination of the advantageous amount in each case being familiar to those skilled in the art.



By adding water-soluble cellulose derivatives to the precipitant, microparticles having a particularly smooth surface may be obtained, the depth of the irregularities on the surface of the microparticles generally being no more than 10% of the mean diameter.

Examples of water-soluble cellulose derivatives are cellulose esters and cellulose ethers, their mixed forms, for example hydroxypropyl methyl celluloses, hydroxyethyl celluloses, carboxymethyl celluloses, cellulose acetates, cellulose butyrates, cellulose propionates, cellulose acetobutyrate, cellulose acetopropionates, cellulose nitrates, ethyl celluloses, benzyl celluloses, methyl celluloses etc.

Mixtures of various water-soluble cellulose derivatives can also be used.

For the purposes of the present invention, the term "water-soluble cellulose derivatives" is taken to mean those components which, according to the definition of the German Pharmacopoeia (DAB = Deutsches Arzneimittelbuch, Wissenschaftliche Verlagsgesellschaft mbH, Stuttgart, Govi-Verlag GmbH, Frankfurt, 9th, Edition 1987), under the category very readily soluble to sparingly soluble.

The concentration of the water-soluble cellulose derivative in the precipitant is no longer critical. The upper limit is given inevitably from the resultant viscosity and thus the processability of the resultant solution.

Concentrations of 2 g of (cellulose derivative)/l (precipitant) to 150 g/l, preferably from 5 g/l to 80 g/l, and in particular 8 g/l to 20 g/l, have proved to be advantageous.

The proportion of particularly small particles having a mean diameter of 1 nm to 2  $\mu$ m can be increased by adding hot-water-soluble poly-alpha-D-glucan to the precipitant.

For this, the same poly-alpha-D-glucan compounds can be used as have been mentioned in connection with the unbranched water-insoluble polyglucan, provided that this complies with the feature hot-water-soluble.

Preferred examples are native or chemically modified starches, poly-alpha-D-glucans produced from these starches, and starch-analog compounds.

5 Starch-analog compounds are taken to mean compounds which consist of poly-alpha-D-glucans, that are not of vegetable origin. An example of this is glycogen or dextran.

The hot-water-soluble poly-alpha-D-glucans can be used as a mixture of one unbranched and one branched fraction, as is present, for example, in starch. In this case, the proportion of unbranched poly-alpha-D-glucan  
10 should be more than 15% by weight, preferably 50 to 99.5% by weight, in particular 60 to 90% by weight, and very particularly preferably 65 to 80% by weight, based on the total amount of poly-alpha-D-glucan in the precipitant.

However, they can also consist of branched structures, as are present, for  
15 example, in amylopectin or in glycogen.

In the context of the present invention, "hot-water-soluble" means that the poly-alpha-D-glucans are essentially insoluble at room temperature, preferably the same measure applying as for the term "water-insoluble" in  
20 connection with unbranched polysaccharides.

The terms "solution" and "solubility" are also taken to mean, in particular, suspensions or the formation of suspensions as occur in the dissolution of starch.  
25

For example, the inventively preferred hot-water-soluble starches show virtually no solubility in water at room temperature, while what are termed the cold-water-soluble starches are more readily soluble under these conditions.

30 The hot-water-soluble starches feature, in particular, the fact that they form solutions during heating to a temperature in the range from about 100 to about 160°C under inherent pressure, for example in an autoclave, the respective temperature depending on the type of starch.

35 For example, potato starch can be boiled to complete dissolution at approximately 100°C, whereas corn starch requires a temperature of approximately 125°C.

For the inventive process, the hot-water-soluble poly-alpha-D-glucans are added to the precipitant preferably at maximum concentration, that is to say a saturated solution is prepared.

- 5 Other suitable ranges are more than 0.001% by weight to 10% by weight, preferably from 0.01 to 2% by weight, and in particular from 0.05% by weight to 0.5% by weight, based on the amount of precipitant used.

10 In the case of thermoplastic polyglucans, the additives can advantageously be added to the thermoplastic mixture as plasticizers or in supplementation to the plasticizers, so that a dry powder mixture is present which can then be processed to be microparticles, the microparticle formation process also being able to take place only in the final formulation with addition of the thermoplastic polyglucans.

15

An extensive description of the microparticles used here, their preparation and the water-insoluble unbranched polyglucans which can be used for this is given in the applicant's German patent applications which have an earlier priority, but which were not published prior to the present application  
20 and have file numbers 197 37 481.6, 198 03 415.6, 198 16 070.4, 198 30 618.0, 198 27 978.7, 198 39 216.8, 198 39 214.1 and 198 39 212.5 which are expressly incorporated by reference into the present description.

25 In addition, the inventively used microparticles are distinguished by a high biocompatibility.

The biocompatibility of the inventively used microparticles, in particular the nature-identical character of the water-insoluble unbranched polyglucans used for the preparation and of their degradation products is of high importance.

30

If not stated otherwise, the percentages by weight for the composition of the oral hygiene products relate to the total weight of the oral hygiene product.

- 35 The inventive oral hygiene products can comprise, depending on type and application, up to 90% by weight, in particular up to 70% by weight, preferably from 2% by weight to 50% by weight, in particular from 15% by

weight to 45% by weight, and particularly preferably from 20% by weight to 25% by weight, of microparticles, based on the total composition.

5 The composition of the inventive oral hygiene products is described in more detail below.

The general makeup of a toothpaste essentially comprises 15-60% by weight of cleaning bodies, up to 40% by weight of moisture retention agents, which are to prevent drying out, up to approximately 2% by weight of binders which result in the viscosity and creamy consistency of the  
10 strand, up to approximately 0.2% by weight of preservatives for preventing bacterial decomposition, in particular of binders and moisture retention agents, up to approximately 2.0% by weight of surfactants, and other additives, such as sweeteners (up to approximately 0.1% by weight) for flavor enhancement, flavorings (up to approximately 1% by weight) and  
15 special active compounds.

Tooth powders principally differ from tooth creams in that they do not contain moisture retention agents, therefore their cleaning body content can be up to 90% by weight.

20

Examples of cleaning bodies which can be used in addition to the inventive microparticles are aluminum hydroxide, calcium carbonate, calcium hydrogen phosphate dihydrate, calcium hydrogen phosphate, silicic acid, sodium aluminum silicates having, for example, a zeolite structure  
25  $(\text{Na}_{12}(\text{AlO}_2)_{12}(\text{SiO})_{12} \cdot 27(\text{H}_2\text{O}))$ , insoluble sodium metaphosphate  $(\text{NaPO}_3)_n$  and hydroxyl apatite.

Examples of moisture retention agents are polyols, such as glycerol, propylene glycol, sorbitol and xylitol.

30

According to a particularly preferred embodiment, in the inventive oral hygiene product, the ratio of microparticles to moisture retention agents, where moisture retention agents are added, is from 4:1 to 1:4, preferably from 3:1 to 1:3, and in particular from 2:1 to 1:2.

35

Examples of binders are, in addition to the inventive microparticles, cellulose derivatives, carrageenan and silicic acids.

Examples of preservatives are 4-hydroxybenzoic esters or sodium benzoate.

5 Examples of sweeteners are saccharin, sodium cyclamate and calcium cyclamate, sorbitol and other sweeteners which are noncariogenic,

Examples of flavorings are peppermint oil, curly spearmint oil, winter green oil, myrrh and, in particular for children's toothpastes, fruit flavorings.

10 Special active compounds can be, for example, fluorine compounds for caries prophylaxes, such as sodium fluorophosphate, alkali metal fluoride, zinc fluoride and quartz ammonium fluorides. In addition, active compounds can be added for care of inflamed gum, such as azulene, allantoin [sic] and bisabolol, and plant extracts (chamomile, myrrh, etc.).

15

To reduce sensitivity, strontium salts, potassium nitrates and citrates can be added.

If the toothpaste or the tooth powder is to act against colored plaques and spots on the teeth, they have a particularly high abrasive content.

20

The toothpaste can be whitened by the inventive microparticles themselves or, if required, if, for example the microparticles are only added in small amounts, in order to act, for example, as carrier for active compounds, by adding titanium dioxide.

25

According to a further embodiment, the inventive oral hygiene product can be a mouthwash. In general, mouthwashes serve less for cleaning the teeth and the oral cavity, but rather for freshening and masking bad breath. In inventive mouthwashes, therefore, the microparticles preferably serve as carrier material for additives such as flavorings, sweeteners and special active hygiene compounds.

30

35

Mouthwashes essentially comprise from 20:1 to about 2:1 of a water/ethyl alcohol solution and other additives such as flavorings, sweeteners, moisture retention agents and surfactants, as have been described above, for example. Examples of surfactants are sodium lauryl sulfate, sodium lauroyl sarcosinate, medical salts, palm kernel fatty acid tauride, sodium

lauryl sulfoacetate, coconut fatty acid monoglyceride sulfonate and betaine.

5 The general makeup of a mouthwash customarily comprises from about 5% by weight to about 60% by weight of ethyl alcohol, up to about 20% by weight of a moisture retention agent, up to about 2.0% by weight of a dispersing aid, up to about 0.5% by weight of sweetener, up to about 0.3% by weight of flavoring and the remainder of water.

10 Owing to the good dispersability of the inventively used microparticles, the inventive mouthwashes are also very particularly suitable for use as mouth sprays in pressurized gas packages.

15 According to a further embodiment, the inventive oral hygiene products can be pastilles and chewing gums for oral hygiene.

Pastilles serve in particular for imparting fresh breath. In this case, the microparticles can be used as tablet binder and additionally act as carrier material for additives such as flavorings etc.

20 Chewing gums for oral hygiene serve in particular for rapid cleaning, where cleaning with a toothbrush is not possible, for example while traveling, and at the same time for masking bad breath. In this case the microparticles can act in particular as cleaning agents and as carrier material for additives such as flavorings and other additives as are customary in chewing gums  
25 of this type. Chewing gums customarily comprise homopolymers and copolymers, such as polyethyl ether, polyvinyl isobutyl ether, polyisobutylene, polyvinyl acetates and others.

30 A further field of application for the inventive oral hygiene products is denture and prosthesis cleaning. Compositions for this are summarized below as "denture cleaners". Denture cleaners are customarily effervescent tablets and powders for dissolution in water. They customarily comprise surfactants, complexing agents, percompounds, pH regulators, compounds releasing carbon dioxide, and other additives, for example enzymes which  
35 promote cleaning by cleaving protein.

When used in denture cleaners, the microparticles can act in particular as carriers of active compounds which release these gradually. This is of

particular importance for long-term cleaning products in which the denture or the prosthesis must remain for several hours, for example overnight.

Clearly, other constituents and formulations can also be used for the inventive oral hygiene products, as are copiously described in the literature. For example, in this context, reference is made to the monograph "Kosmetik, Entwicklung, Herstellung und Anwendung kosmetischer Mittel" [Cosmetics, development, production and use of cosmetic compositions], edited by Wilfried Umbach, pages 181 to 223, (1988) Georg Thieme Verlag Stuttgart, New York, and "Kosmetische Mittel zur Zahn- und Mundpflege" [Cosmetic products for dental and oral hygiene] in Hagers Handbuch der pharmazeutischen Praxis [Hager's handbook of pharmaceutical practice], 5th Edition, pages 191 to 197.

These references give other examples of the abovementioned components of oral hygiene products and examples of formulations as can also be used in principle for the present invention.

The present invention is described below with reference to individual exemplary embodiments, these examples being intended to illustrate the invention and not to restrict the present invention.

### **Example 1**

In-vitro production of an unbranched water-insoluble poly-1,4- $\alpha$ -D-glucan in a biocatalytic process using amylosucrase.

25 15 l of a 20% strength sucrose solution are added to a sterilized (steam sterilization) 25 l vessel. 120 ml of enzyme extract containing amylosucrase is added in one portion. The enzyme activity in this experiment is 20 units (1 unit = 1  $\mu$ mol of sucrose  $\times$  min<sup>-1</sup>  $\times$  mg of enzyme). The apparatus is fitted with a KPG stirrer, which has also been sterilized. The vessel is closed, kept at 39°C and stirred. Even after only a few hours, a white precipitate forms. The reaction is ended after a period of 54 hours. The precipitate is filtered off and washed twice with water to remove low-molecular-weight sugars. The residue remaining in the filter is dried at 38°C in a drying cabinet, with a vacuum being applied by a diaphragm pump (Vacuubrand GmbH & Co., CVC 2). The mass is 893 g (yield 59%). (Molecular weights:  $M_w$  = 9000 g/mol;  $M_n$  = 4400 g/mol;  $M_w/M_n$  [sic] = 2.05; GPC, solvent DMSO, calibration using pullulan standards).

**Example 2**

Production of microparticles from poly-1,4- $\alpha$ -D-glucan

200 g of poly-1,4- $\alpha$ -D-glucan are dissolved within [sic] rapidly at 50°C in  
5 about 1 l of dimethyl sulfoxide (DMSO, analytical grade from Ridel-de-  
Haen). The solution is added slowly by a dropping funnel to 8 l of twice-  
distilled water with stirring. The batch is stored overnight at 4°C. The fine  
suspension of particles is removed by decanting. The bottom sediment is  
suspended and centrifuged (ultracentrifuge RC5C: 5 minutes each time at  
10 5000 rpm). The solid residue is slurried with twice-distilled water and  
centrifuged a total of three times. The solids are collected and the still-  
moist suspension of approximately 1000 ml is freeze-dried (Christ Delta 1-  
24 KD). 176 g of white solid are isolated (yield 88%). The surface of the  
particles is of spherical shape. The majority of the particle diameters are in  
15 the range of 2-3  $\mu$ m. The specific surface area is 3.75 m<sup>2</sup>/g (method:  
Sorptomatic 1990 (Fisons Instruments)).

**Example 3**

20 500 mg of poly-1,4- $\alpha$ -D-glucan are dissolved at approximately 70°C in  
about 2.5 ml of dimethyl sulfoxide (DMSO, analytical grade from Riedel-de-  
Haen). The DMSO solution is added dropwise to 100 ml of twice-distilled  
water with stirring and the solution is kept overnight at 5°C. The fine milky  
suspension is centrifuged for 15 minutes at 3500 rpm and the supernatant  
25 is decanted off. The bottom sediment is slurried with twice-distilled water  
and centrifuged again. The procedure is repeated another two times. The  
suspension is then freeze-dried. 311 mg of white poly-1,4- $\alpha$ -D-glucan  
particles are obtained. This is equivalent to a yield of 62% of colorless  
microparticles.

30

**Example 4**

Production of toothpastes using the microparticles of Example 2

Two toothpastes having the composition according to the table below were  
35 assessed.

Both toothpastes showed excellent cleaning results, did not change in  
consistency even after a relatively long time opened and were rated very



positively in a subjective rating by test persons with respect to their sensory properties, for example feel during teeth cleaning.

Component	Content (% by weight)	
	Example a	Example b
Carboxymethyl cellulose	1.5	1.5
Glycerol	40.0	30.0
Titanium dioxide	2.0	2.0
Calcium carbonate	5.0	7.5
Sodium dodecyl sulfate (SDS)	1.0	1.0
Microparticles	20.0	17.5
Remainder water		

## Patent claims

1. An oral hygiene product which comprises as essential constituents spherical microparticles which consist in whole or in part of at least one water-insoluble unbranched polyglucan.  
5
2. The oral hygiene product as claimed in claim 1, wherein the spherical microparticles have a mean diameter of from 1 nm to [lacuna]  $\mu\text{m}$ .  
10
3. The oral hygiene product as claimed in claim 1 or 2, wherein the depth of irregularities on the particle surface is a maximum of 20% of the mean diameter of the spherical microparticles.
- 15 4. The oral hygiene product as claimed in one of the preceding claims, wherein the microparticles are present in the oral hygiene product in an amount of up to 90% by weight, based on the total weight of the oral hygiene product.
- 20 5. The oral hygiene product as claimed in one of the preceding claims, wherein the at least one water-insoluble polyglucan is poly-1,4- $\alpha$ -D-glucan and/or poly-1,3- $\beta$ -D-glucan, in particular poly-1,4- $\alpha$ -D-glucan.
- 25 6. The oral hygiene product as claimed in one of the preceding claims, wherein the at least one water-insoluble unbranched polyglucan has been obtained by a biotechnology method.
7. The oral hygiene product as claimed in one of the preceding claims, wherein the at least one water-insoluble polyglucan as been  
30 produced biocatalytically.
8. The oral hygiene product as claimed in one of the preceding claims, wherein the content of water-insoluble unbranched polyglucan in the microparticles is at least 70%, based on the total content of polyglucan including any branched polysaccharide and other  
35 polymers.

9. The oral hygiene product as claimed in one of the preceding claims, wherein the microparticles consist of 100% of at least one water-insoluble unbranched polyglucan.
- 5 10. The oral hygiene product as claimed in one of the preceding claims, wherein oral hygiene product is selected from mouthwashes, mouth powders, mouth pills, mouth sprays, denture, prosthesis and dental hygiene products and plaque disclosure tablets.
- 10 11. The oral hygiene product as claimed in claim 10, wherein the dental hygiene product is selected from toothpastes, tooth gels, tooth-cleaning powders and chewing gums.
- 15 12. The use of microparticles which consists in whole or in part of at least one water-insoluble unbranched polyglucan in dental hygiene products.

Abstract

Oral hygiene product comprising spherical microparticles based on unbranched water-insoluble polyglucans

The present invention relates to oral hygiene products, which comprise as essential constituents spherical microparticles, which consist in whole or in part of at least one water-insoluble unbranched polyglucan.